



Armed Forces College of Medicine AFCM





Cardiopulmonary Module

Biochemical Basis

of

Cardiopulmonary Diseases

By

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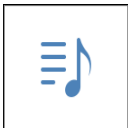
Biochemistry





By the end of this lecture the student will be able to:

1. Describe the structure of elastin and pulmonary surfactant.
2. Explain the biochemical basis of cystic fibrosis, α 1 antitrypsin deficiency and respiratory distress syndrome.
2. Correlate the signs and symptoms to the



Cystic Fibrosis (CF)

Outline

What is cystic fibrosis (CF)?

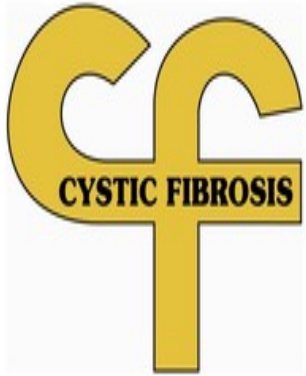
What causes CF?

What are the manifestations?

How do you diagnose CF?

How do you treat CF?





What is cystic fibrosis (CF)?

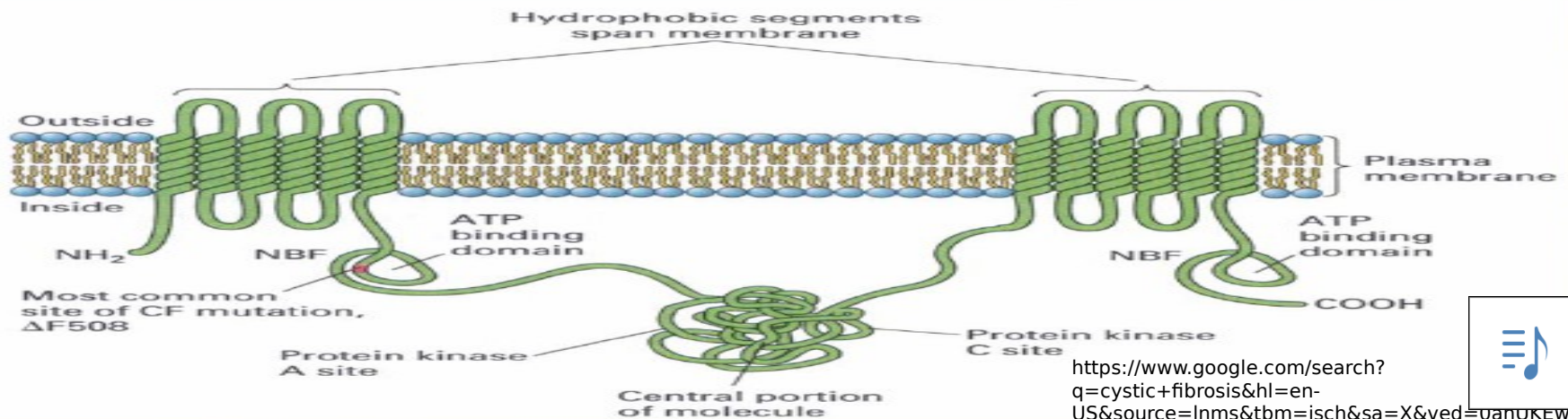
Chronic, progressive and life limiting **autosomal recessive** genetic disease characterized by chronic respiratory disease, pancreatic insufficiency, elevation of sweat electrolytes and male infertility



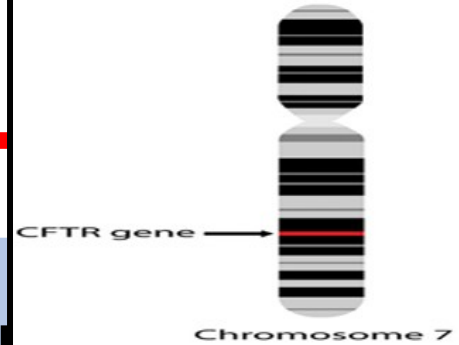
What causes CF?

Defect in the gene that encodes a membrane protein called cystic fibrosis transmembrane conductance regulator, or **CFTR**

CFTR



Genetics of CF (1)



**The most common mutation
3 base pair deletion leading to absence of
phenylalanine at position 508 ($\Delta F508$) of
the CFTR protein**

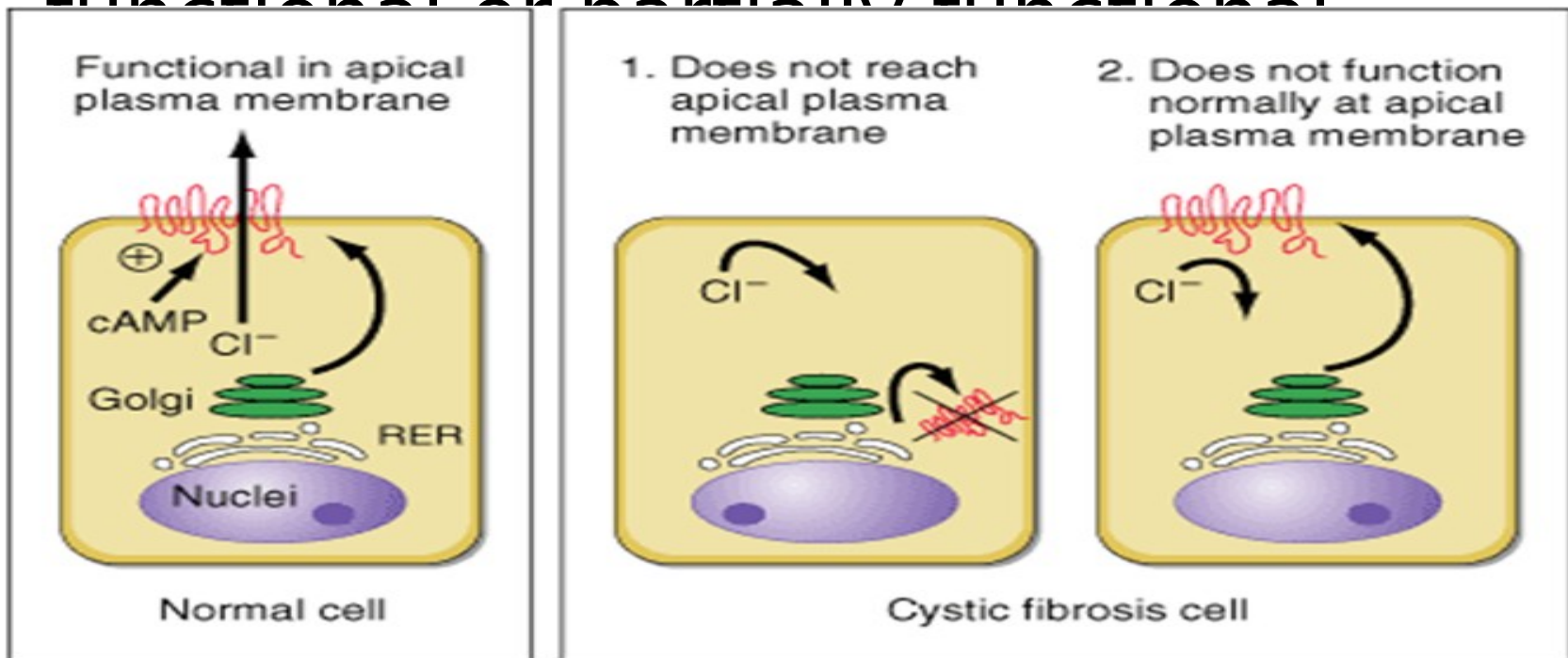
**The mutant protein is not correctly
maturing and reaching the plasma
membrane**

**$\Delta F508$ mutation leads to improper
processing and intracellular degradation of
the CFTR protein**



Genetics of CF (2)

Other mutations in the CF gene produce fully processed CFTR proteins that are either non-functional or partially functional



The CFTR protein

- Single polypeptide chain
- Found in the plasma membrane of normal epithelial cells
- cAMP regulated chloride channel
(The channel is normally closed but opens when phosphorylated by protein kinase A, thus providing regulated chloride and fluid secretion)
- Regulator of other ion channels



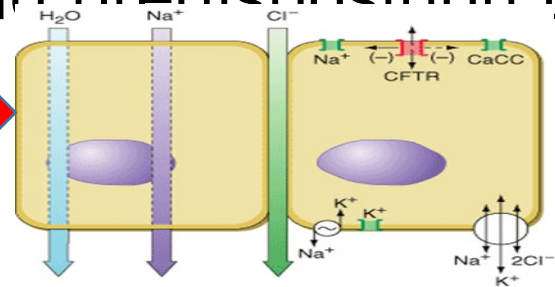
Pathophysiology

Lung

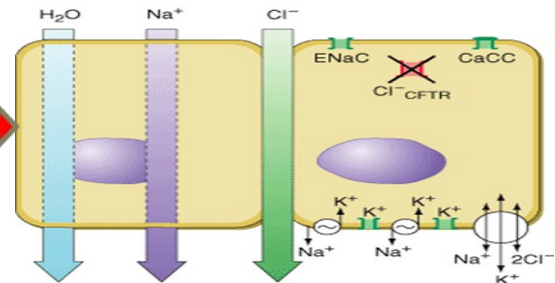
High rate of sodium absorption and low rate of chloride secretion reduces salt and water content in mucus

Mucus adheres to airway surface, leads to decreased mucus clearing and predisposition to infections

Normal airway epithelia



CF altered airway epithelia



Pathophysiology

Pancreas:

Absence of CFTR limits function of chloride-bicarbonate exchanger to secrete bicarbonate

Leads to retention of enzymes in the pancreas, destruction of pancreatic tissue.



Pathophysiology

Intestine

Decrease in water secretion leads to thickened mucus and obstruction of small and large intestines

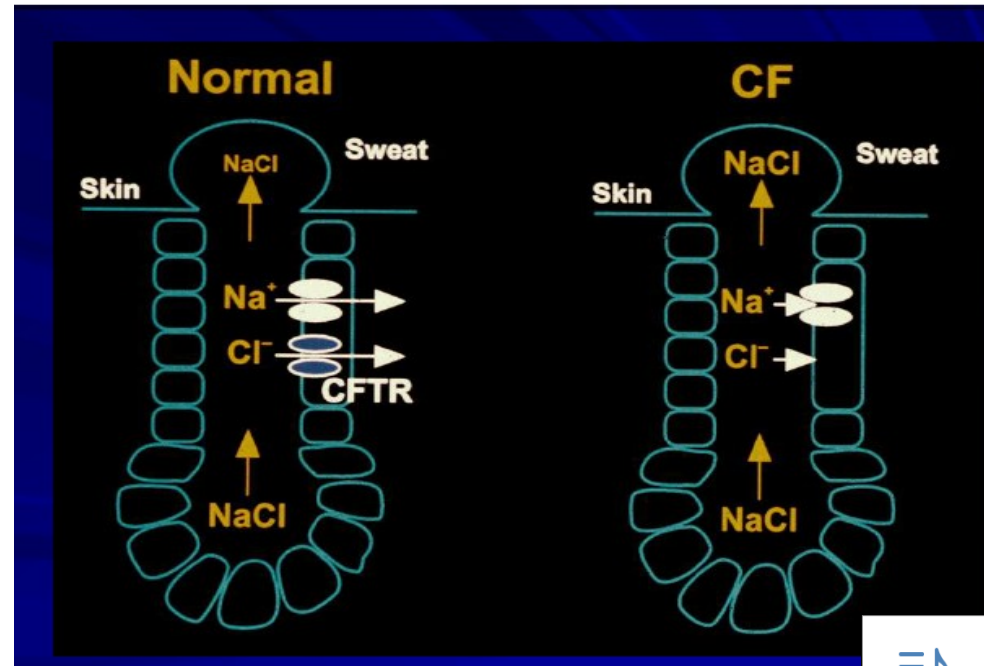


Pathophysiology

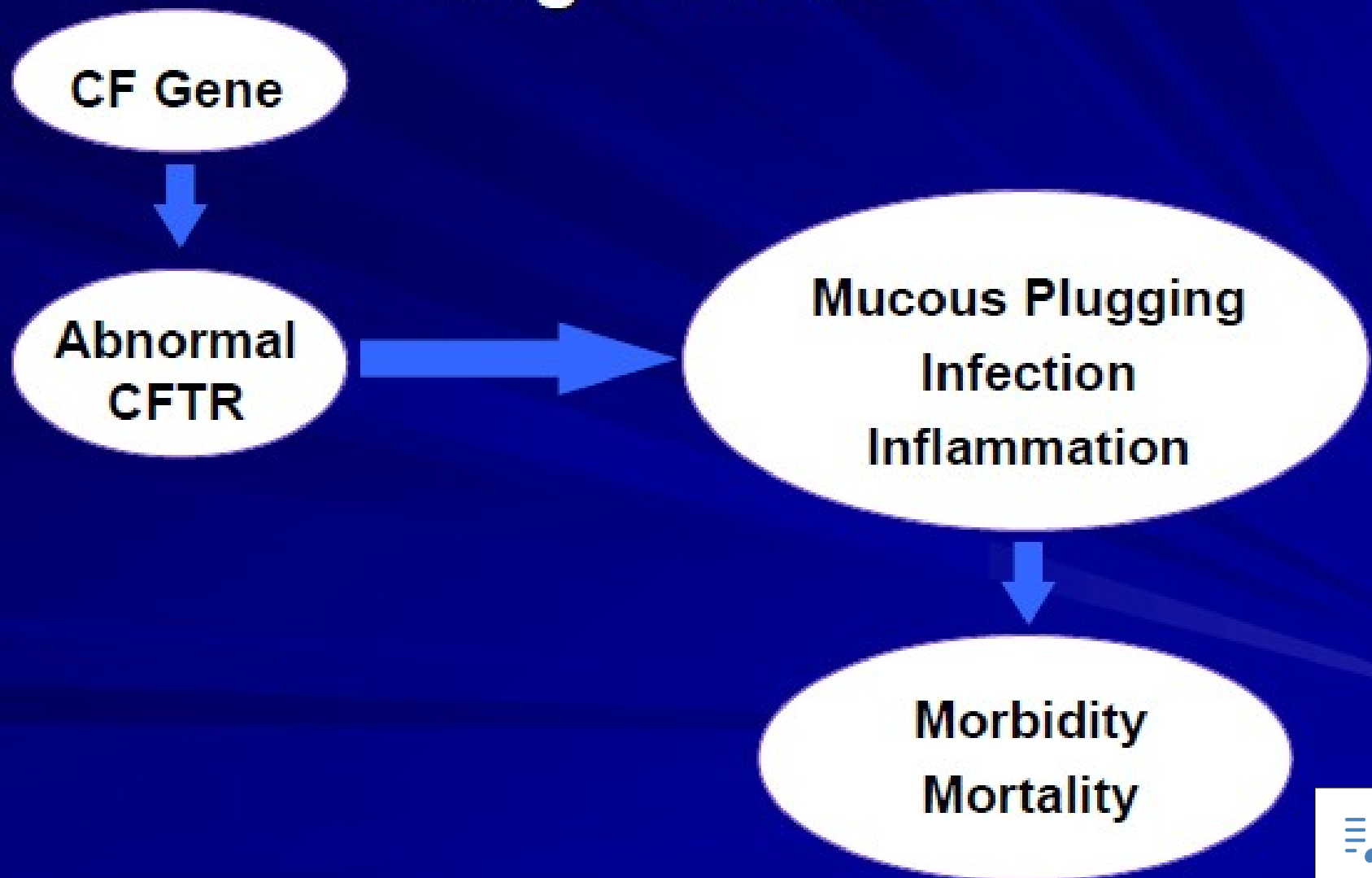
Sweat:

Normal volume of sweat

Inability to reabsorb NaCl from sweat as it passes through sweat duct



Pathogenesis of Cystic Fibrosis Lung Disease



Clinical Picture of Cystic Fibrosis

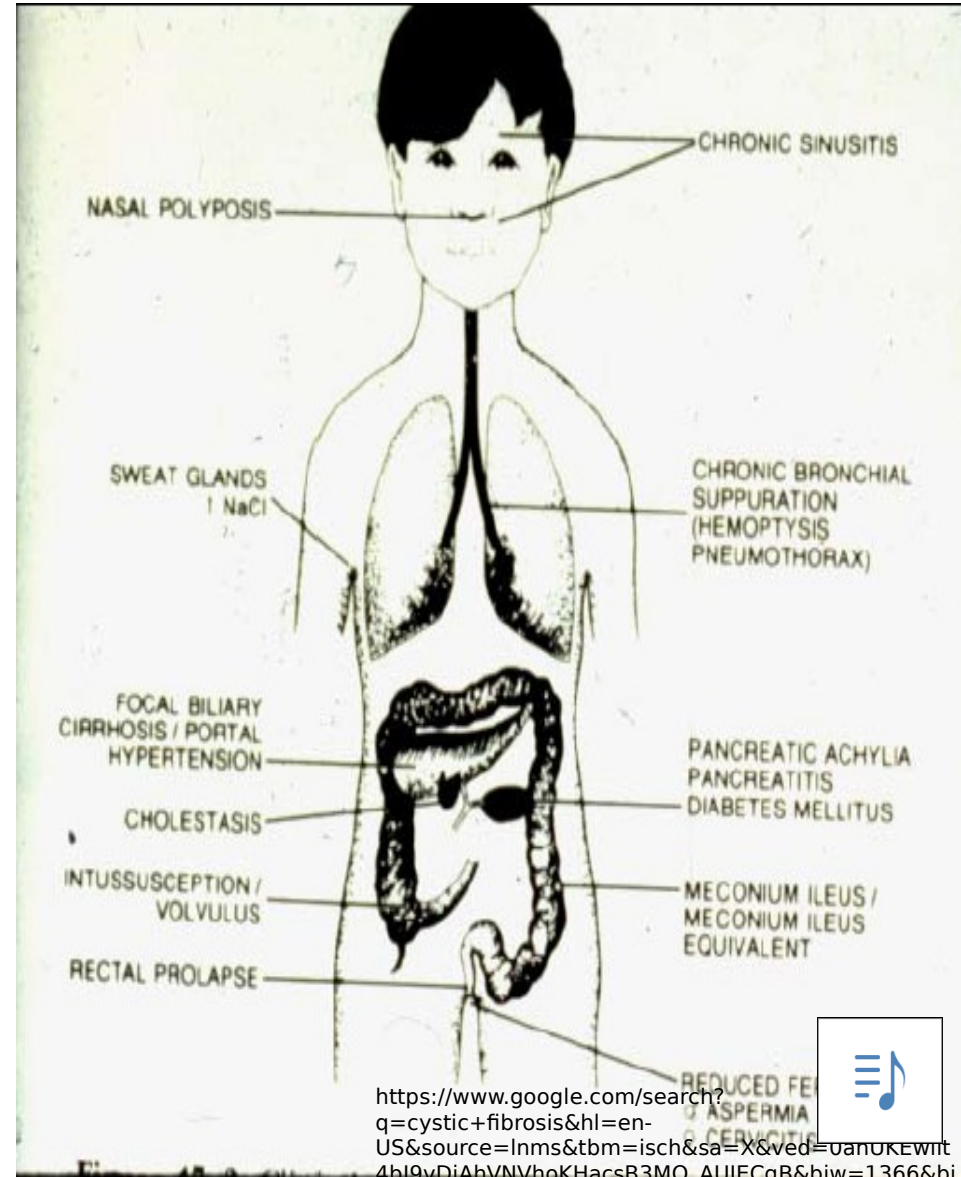
Impaired lung clearance of mucous

Recurrent lung infection and inflammation

Pancreatic damage

Impaired digestion

Infertility



Diagnosis

- 1) Presence of typical clinical features**
- 2) History of CF in a sibling**
- 3) Positive newborn screening test**
- 4) Plus laboratory evidence for CFTR dysfunction:**
 - Two elevated sweat chloride concentrations on two separate days (>70 mEq/L)**
 - Identification of two CF mutations**



Treatment

Major objectives

Promote clearance of secretions

Control lung infection

Provide adequate nutrition

Prevent intestinal obstruction

**Investigation into therapies to
restore the processing of misfolded
CFTR protein**



Answer the following question

Cystic fibrosis is caused by which of the following?

- A. A defective gene that leads to the making of an abnormal protein
- B. Someone who eats too much salt
- C. A defective gene that causes abnormalities in the brain
- D. The cause is not known

Elastin

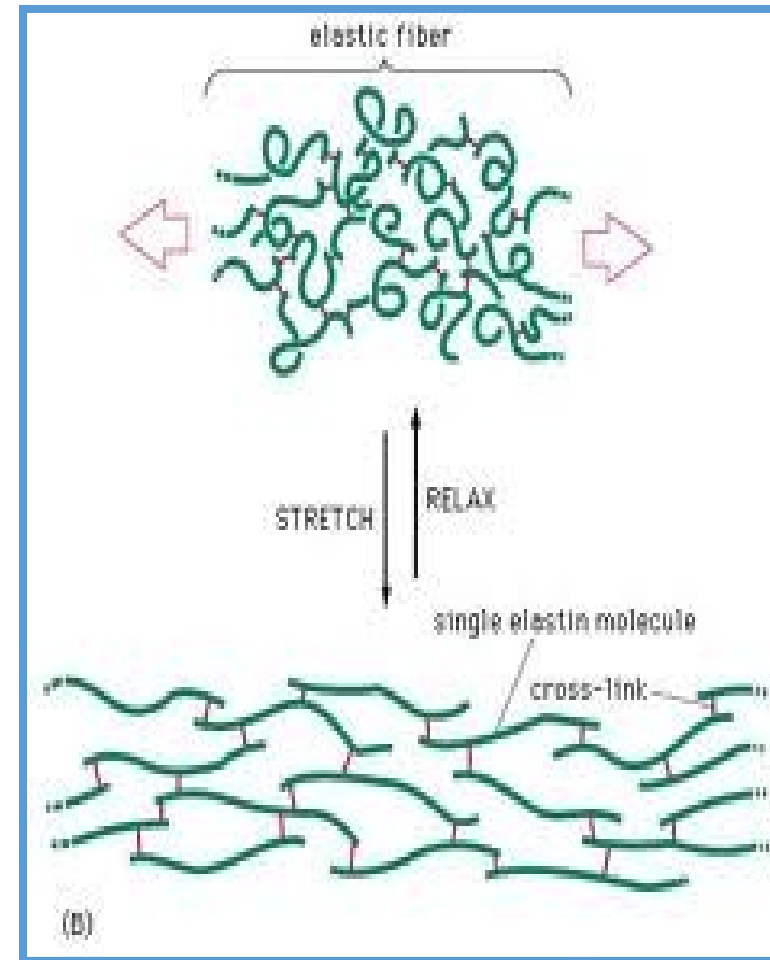
Elastin fibers are found in:

- Lungs
- Walls of large arteries
- Elastic ligaments



Elastin provides elasticity

Elastin fibers are highly branched that can be stretched to several times their normal length and recoil to their original shape when stretching force is relaxed



Structure of elastin

- The basic unit (precursor) of elastin fibers is tropoelastin
- Tropoelastin is linear polypeptide composed of about 700 AAs that are primarily small and nonpolar (eg glycine, valine and alanine)
- Elastin is rich in lysine and proline, little hydroxyproline and hydroxylysine



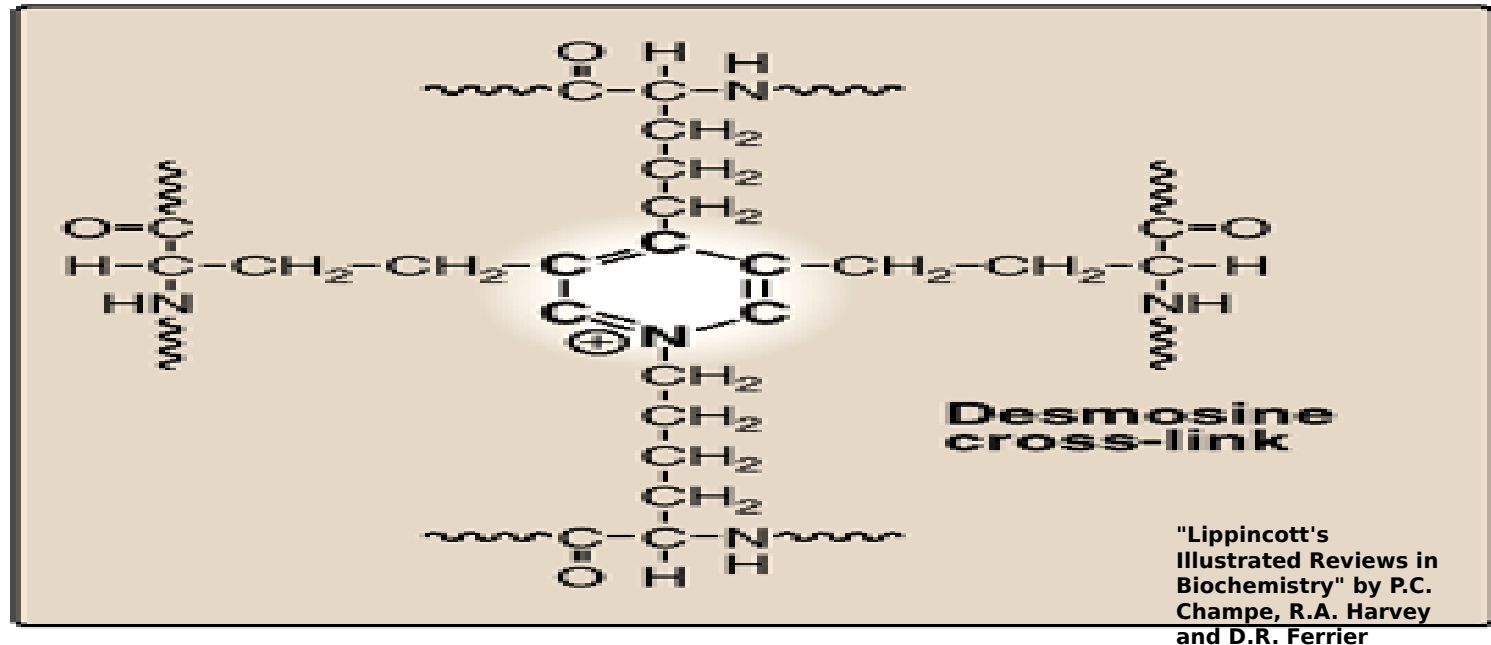
Structure of elastin

- In the extracellular space, tropoelastin interacts with microfibrils, such as fibrillin, which function as scaffold into which tropoelastin is deposited
- Covalent cross links connect elastin polypeptide chains into a network
- The cross links may occur within the same polypeptide chain or involve 2 to 4 different polypeptide chains
- The cross links also involve desmosine



Desmosine

- It is a heterocyclic structure formed of 3 allysine residues with one lysine.



N.B. Allysine residues are formed through oxidative deamination of lysyl side chains of tropoelastin by lysyl oxidase enzyme



α 1 antitrypsin (AAT)

Most AAT found in plasma is synthesized and secreted by the liver

Extrahepatic synthesis occurs in monocytes and alveolar macrophages (important in the prevention of local tissue injury by elastase)

Is also present in blood and other body fluids

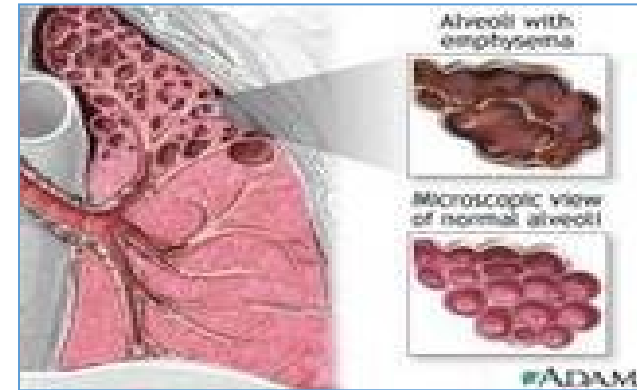


Role of $\alpha 1$ antitrypsin in the lungs

It inhibits proteolytic enzymes including elastase enzyme which is secreted by neutrophils and degrades elastin of alveolar walls as well as other structural proteins in a variety of tissues



α 1 antitrypsin deficiency (1)



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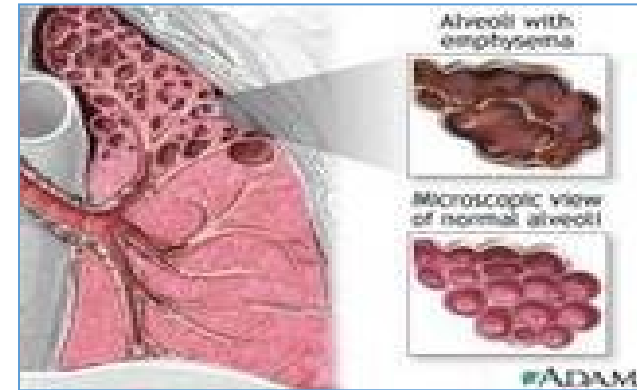
Results from different mutations of AAT gene causing deficiency of the protein

The most clinically widespread is one single purine base mutation (GAG to AAG, resulting in the substitution of lysine for glutamic acid at position 342 of the protein)

The mutation causes the normally monomeric AAT to polymerize within the endoplasmic reticulum of hepatocytes, resulting in decreased secretion of AAT from the liver



α 1 antitrypsin deficiency (2)



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Consequently, the polymer that accumulates in the liver may result in cirrhosis and the blood levels of AAT are reduced, decreasing the amount that gets to the alveoli

This causes loss of elastase enzyme inhibition resulting in degradation of elastin of alveolar walls inducing a disease called emphysema



Smoking and Emphysema

Methionine 358 in AAT is required for the binding of the inhibitor to its target proteases.

Smoking causes the oxidation and subsequent inactivation of the methionine, thereby rendering the inhibitor powerless to neutralize elastase.

Smokers with AAT deficiency, therefore, have a considerably elevated rate of lung destruction and a poorer survival rate than nonsmokers with the deficiency.



Emphysema

Emphysema is a type of COPD involving damage to the alveoli in the lungs.

As a result, your body does not get the oxygen it needs.

Emphysema makes it hard to catch your breath.

The patients may also have a chronic cough and have trouble breathing during exercise.



Diagnosis of Emphysema

- Alpha-1 Antitrypsin Test
- Lung Function Tests
- Spirometry



Treatment of α 1 antitrypsin deficiency

- **Can be treated by IV administration of α 1 antitrypsin**



Answer the following question

α 1 antitrypsin is mainly synthesized in which of the following organs?

- A. Kidneys
- B. Liver
- C. Intestines
- D. Brain

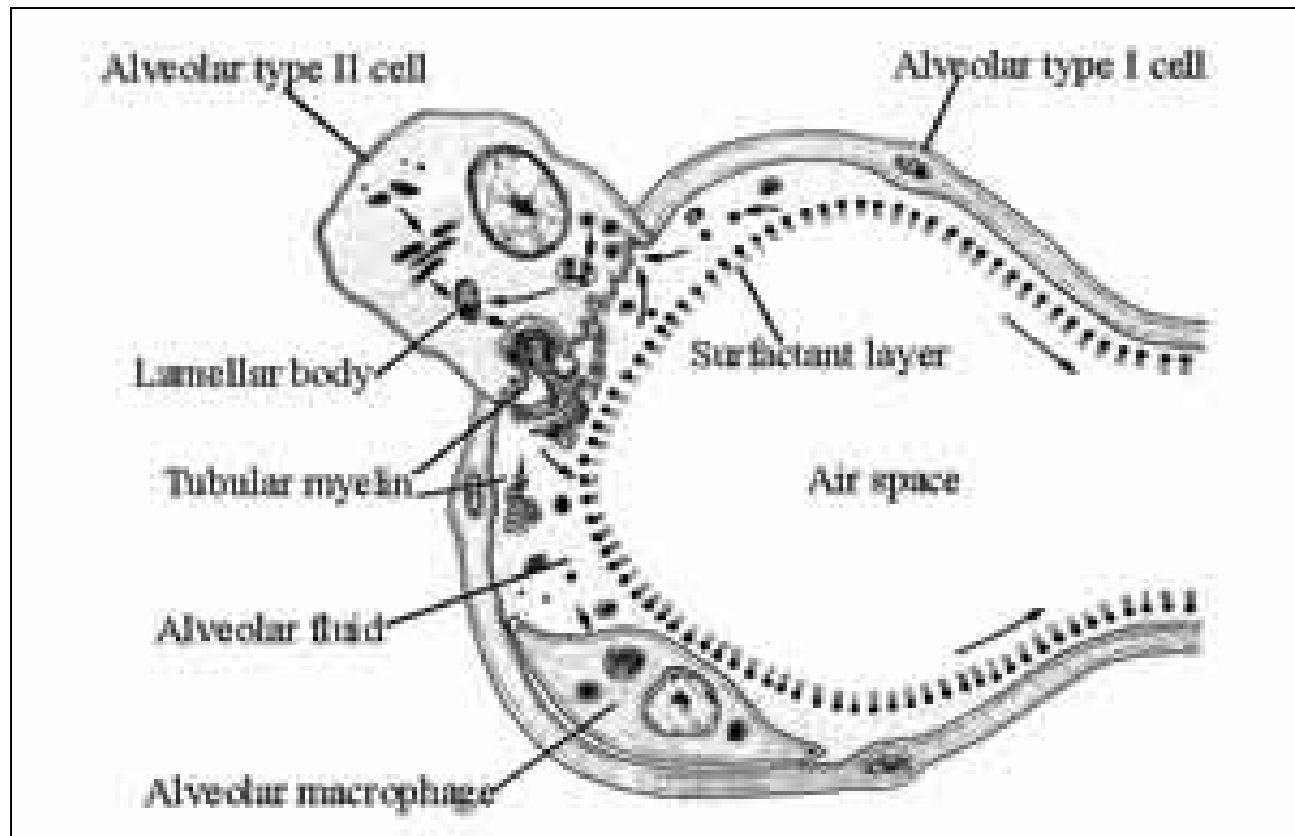
Lungs

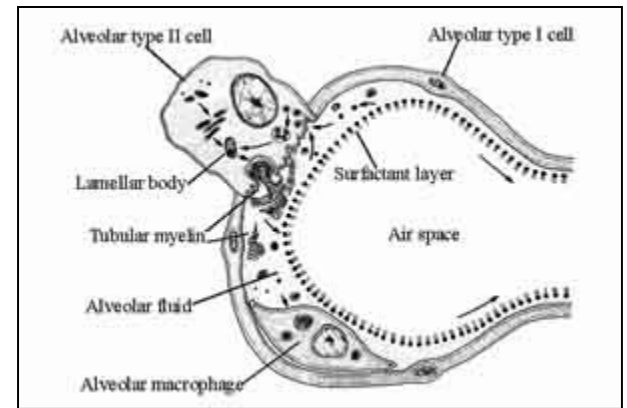


Gas exchange in the lung takes place in the alveoli. Oxygen diffuses from the alveoli to the capillaries, and carbon dioxide leaves the capillaries and diffuses into the alveoli.



Alveoli





- The surface tension of the moist inner surface originates from the attraction between the molecules of the alveolar fluid.
- Without prevention this would result in lung collapse.
- Surfactant lowers the surface tension at the alveolar air-fluid interface



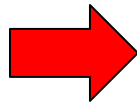
Composition of pulmonary surfactant

**Lipids
(90%)**

**Proteins
(10%)**

**Phosphatidyl choline
(80%)**

**Dipalmitoylated
(60%)**



Dipalmitoyl Phosphatidylcholine

1-

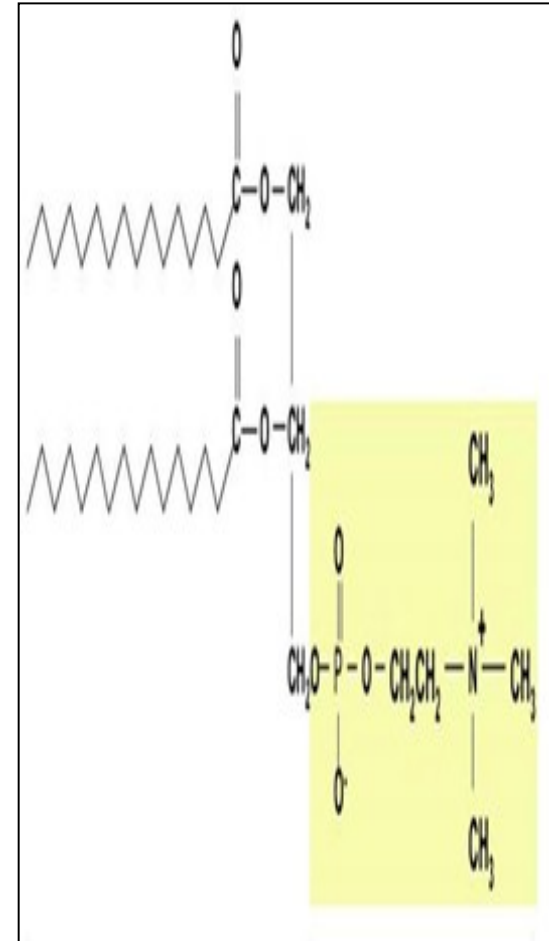
- **Glycerol**

2-

- **Palmitic acid at C1&2**

3-

- **Phosphoric acid and choline.**





- In premature babies, the lungs are developmentally deficient in lung surfactant



Adult respiratory distress syndrome

- is a medical condition occurring in critically ill patients characterized by widespread inflammation in the lungs.
- It results in injury of the cells that form the alveolar barrier, surfactant dysfunction, activation of the innate immune response, and abnormal coagulation.
- Is characterized by impaired gas exchange within the lungs



Treatment



Answer the following question

Which of the following is an accurate statement about lung surfactant?

- A. Prevents air trapping during expiration
- B. Raises surface tension in the alveolus
- C. Is manufactured in the white blood cells
- D. Contains lecithin

Key points

- Cystic fibrosis is caused by mutations in the gene encoding the CFTR protein, a Cl⁻ transporter.
- Cystic fibrosis is characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The disorder's most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems.
- Cystic fibrosis may be diagnosed by many different methods, including newborn screening, sweat testing, and genetic testing.
- Alpha-1 antitrypsin deficiency is a genetic disorder that may result in lung disease or liver disease. Affected individuals often develop emphysema. Smoking or exposure to tobacco smoke accelerates the appearance of emphysema symptoms and damage to the lungs.

References

- **Fundamentals of Clinical Chemistry (Tietz) Sixth**
- **"Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin**
- **"Lippincott's Illustrated Reviews in Biochemistry" by P.C. Champe, R.A. Harvey and D.R. Ferrier**
- **"Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell.**



A close-up photograph of a bouquet of red felt roses. The roses are made of a textured, felt-like material and are arranged in a cluster. Green felt leaves are interspersed among the roses. The background is a plain, light-colored surface.

thank you

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